Gemcitabine/Carboplatin Combination Regimens: Importance of Dose Schedule

Published on Psychiatric Times
(http://www.psychiatrictimes.com)

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Platinum compounds, either cisplatin (Platinol) or carboplatin (Paraplatin), in combination with a number of new chemotherapeutic agents, have demonstrated improved response or survival compared to cisplatin alone or older

Introduction

Platinum compounds remain the cornerstone of chemotherapy for advanced non-small-cell lung cancer (NSCLC). A number of randomized trials and meta-analyses have concluded that platinum-based therapy results in improved survival, symptom control, and quality of life compared to supportive care alone.[1-3] In a Cox multivariate analysis of approximately 2,300 cases of advanced NSCLC treated in studies conducted by the Southwest Oncology Group (SWOG), platinum-based chemotherapy was found to be an independent predictive factor for improved survival, along with performance status and female gender.[4] More recently, studies of several new chemotherapeutic agents, such as gemcitabine (Gemzar), paclitaxel (Taxol), docetaxel (Taxotere), vinorelbine (Navelbine), and irinotecan (Camptosar), have demonstrated better single-agent activity in NSCLC than that observed with platinum compounds or other chemotherapeutic agents previously available.[5] Phase II trials of these new agents in combination with cisplatin (Platinol) or carboplatin (Paraplatin) have subsequently reported impressive response and survival data.[6] In randomized phase III trials, these combinations have yielded improved response rates and/or survival compared to cis-platin alone or older platinum-based combinations.[7-10] As a result, these studies have changed what is regarded as the optimal therapy for advanced-stage NSCLC. At present, none of these new regimens has proven to be superior, leaving several alternative therapeutic options for the treatment of advanced NSCLC. A number of issues remain unresolved for each of these regimens (Table 1).

The nucleotide analog, gemcitabine, is one of the most promising of the new chemotherapeutic agents. In addition to reproducible single-agent activity with response rates of approximately 20% in several phase II trials, two randomized studies have demonstrated that single-agent gemcitabine produces survival equivalent to that achieved with combinations of cisplatin and etoposide.[11,12] However, gemcitabine has proven to be most efficacious against NSCLC when administered in combination with cisplatin.[8,13,14] Combinations of gemcitabine and cisplatin are attractive theoretically because of the observed preclinical synergism, possibly related to reduced repair of platinum-induced DNA damage, a recognized mechanism of platinum resistance.[15] The most common dosing schedule employed has been gemcitabine delivered on days 1, 8, and 15, with cisplatin delivered on either day 1, 2, or 15. Although the toxicity of these combinations has varied somewhat depending on the day cisplatin is administered, thrombocytopenia has typically been dose-limiting.

Gemcitabine and Carboplatin Combinations

Carboplatin appears to be equally efficacious to cisplatin in the treatment of advanced NSCLC. In a randomized trial by the European Organization for Research and Treatment of Cancer (EORTC), the combination of carbo-platin/etoposide produced activity equivalent to that of cisplatin/etoposide.[16] When single-agent carboplatin was compared with several cisplatin-containing combinations in a phase III Eastern Cooperative Oncology Group (ECOG) trial, carboplatin produced the longest survival time, despite a response rate of only 9%.[17]
In these early studies, carboplatin administration was calculated according to body surface area (mg/m²). Because carboplatin is highly excreted renally, dosing by body-surface area resulted in relative underdosing in patients with normal renal function, and overdosing in those with impaired renal function. More recently, clinical trials have delivered carboplatin at a target area under the curve (AUC) according to the Calvert formula (dose in mg = AUC [glomerular filtration rate + 25]),[18] resulting in more appropriate dosing of this agent.

Carboplatin provides an improved therapeutic index compared to cisplatin, especially in terms of reduced nonhematologic toxicities. However, added hematologic toxicity may be problematic when combining carboplatin with other myelosuppressive chemotherapeutic agents. One of the earliest trials to evaluate the combination of gemcitabine and carboplatin in NSCLC was conducted by Carmichael and colleagues.[19] This phase I trial was designed to determine the maximum-tolerated dose (MTD) of carboplatin when administered prior to gemcitabine 1,000 mg/m² on days 1, 8, and 15 of a 28-day cycle. The MTD of carboplatin was an AUC of 5.2 mg/mL × min, as calculated by the Calvert formula. Myelosuppression was dose-limiting, with grade 3-4 neutropenia occurring in 58% of cycles and grade 3-4 thrombocytopenia in 35% of cycles. The reverse sequence of drug administration produced similar results.

Subsequently, Ng et al from Indiana University treated seven chemotherapy-naive patients with advanced NSCLC with a 28-day schedule of gemcitabine (1,000 mg/m² weekly for 3 weeks) followed by carboplatin (AUC = 5).[20] Grade 4 thrombocytopenia was observed in three of five patients evaluable for toxicity. There were no clinical sequelae reported. Nevertheless, these investigators concluded that thrombocytopenia precluded further development of this gemcitabine and carboplatin combination.

Alternative dosing schedules of gemcitabine and carboplatin are now being investigated with encouraging results. One approach has been the development of a 21-day schedule, with carboplatin administered on day 1 and gemcitabine on days 1 and 8, similar to the gemcitabine-cisplatin regimen used by Cardenal et al.[21] The rationale is that grade 4 thrombocytopenia is common with 28-day schedules combining gemcitabine with cisplatin, necessitating omission of the day 15 gemcitabine dose in over 50% of courses.

In studies of the 28-day schedule conducted by Sandler[8] and Crino,[14] grade 4 thrombocytopenia was observed in 28% and 38% of patients, and 22% and 15% of patients received platelet transfusions, respectively. However, with the 21-day schedule reported by Cardenal,[21] grade 4 platelet toxicity occurred in only 16% of cases, and only 3% required platelet transfusion (Table 2). These data support further study of similar dose schedules of gemcitabine/carboplatin combinations. In a trial by Carrato et al,[22] patients with advanced NSCLC were treated with carboplatin at an AUC of 5 and gemcitabine (1,000 mg/m²) administered either on day 1, 8, and 15 of a 28-day cycle, or day 1 and 8 of a 21-day cycle. While these regimens proved to be equally efficacious, hematologic toxicity, especially severe thrombocytopenia, occurred much more frequently with the 28-day cycle (51% vs 17%) (Table 3). This difference in toxicity was observed despite a greater delivered dose intensity with the 21-day cycle.

Similarly, a pilot study of sequential combination chemotherapy by Edelman et al at the University of California Davis Cancer Center used a 21-day schedule with gemcitabine at 1,000 mg/m² administered on days 1 and 8 and carboplatin administered at an AUC of 5.5 for three cycles prior to sequencing to single-agent paclitaxel.[23] This gemcitabine/carboplatin regimen was well tolerated in the majority of patients, with nadir thrombocytopenia occurring on day 15 (a nontreatment day), and recovery by day 21 (Figure 1). Grade 4 thrombocytopenia was observed in 19% of patients, without significant bleeding sequelae.

This level of thrombocytopenia is less than that seen with 28-day regimens of gemcitabine/cisplatin or gemcitabine/carboplatin, and comparable to that seen with 21-day gemcitabine/cisplatin regimens such as that by Cardenal et al (Table 4).[21] The overall response rate was 31% (confidence interval [CI], 13%-53%), and the median survival was 10 months.

Subsequently, this regimen of sequential gemcitabine-carboplatin followed by paclitaxel has been investigated as one arm of SWOG randomized phase II trial evaluating the concept of sequential combination chemotherapy (Figure 2).[24] If encouraging results are obtained, this SWOG trial (S9806) would provide the basis for testing sequential vs concurrent three-drug combinations, with the object of determining which approach provides the greatest therapeutic index in the palliative management of advanced NSCLC.

Conclusions
These studies demonstrate the feasibility and tolerability of combining gemcitabine and carboplatin using alternative dosing schedules. To further evaluate this combination, a National Coalition phase III trial is in development that will compare the University of California Davis Cancer Center regimen of gemcitabine/carboplatin to two other new combinations: paclitaxel/carboplatin and the nonplatinum regimen of gemcitabine/paclitaxel (Figure 3).

Based on the therapeutic ratio of efficacy to toxicity, it is likely that additional new studies investigating gemcitabine/platinum combinations, which employ either cisplatin or carboplatin, will use a 21-day schedule. Gemcitabine will be administered on day 1 and 8, or other alternative dose-schedules will be designed to avoid excessive myelosuppression.

In summary, gemcitabine/cisplatin has proven to be one of the most effective new combination chemotherapy regimens available for the treatment of NSCLC. The platinum derivative carboplatin offers potential therapeutic advantages in terms of reduced toxicity and efficacy equal to cisplatin. Further studies of gemcitabine in combination with carboplatin are clearly warranted.

References:


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